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### REMARKS

Applicants note that claims 1-137 are correctly indicated as pending in the Office Action Summary. These claims stand subject to a restriction requirement based on said Official Action. Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested.

It is noted at the outset that claims 22, 32, 47, 87, 100 and 109 have been canceled and claims 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 15-18, 20, 23-25, 27-31, 33-35, 46, 48-50, 52, 54, 56-59, 73, 76, 78-80, 82, 84-86, 88-90, 99, 101-103, 107, 110-112 and 127-136 have been amended herein. The claims have been amended to correct grammatical errors and to recite specific fragments of the integrin  $\alpha 10$  including cytoplasmic domain, the I-domain and the spliced domain. Basis for the amendments to the claims may be found throughout the specification and claims as filed, especially on page 2, lines 7-18 and page 8, lines 17-37. Applicants reserve the right to file a continuation or division application to pursue the subject matter of the canceled claims. No prohibited new matter is believed to have been introduced by this Amendment.

#### I. Election

Applicants provisionally elect Group I (claims 1, 22-25, 76 and 126, drawn to recombinant or isolated collagen binding integrin subunit  $\alpha 10$  comprising the amino acid of SEQ ID NO:2), with traverse, to comply with the requirements of a complete response to the restriction.

As Group I has been elected, with regard to species, Applicants provisionally elect the amino acid sequence from about amino acid No. 140 to about amino acid No. 337 of SEQ ID NO:2 (as recited in claim 25), with traverse.

Applicants request withdrawal of the restriction or at least modification of the restriction in light of the provisional election arguments set forth below.

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## II. Traversal

Applicants have amended the claims to recite fragments of the integrin α10 including the cytoplasmic domain, the I-domain and the spliced domain. The amendments to the claims is not an admission by Applicants that the subject matter of those claims was distinct or independent or lacks a special technical feature. The amendments are merely submitted in an effort to expedite prosecution of the application. Based on this response, Applicants respectfully request at least reconsideration of the restriction requirement, and provide the following comments.

First Applicants address the Restriction Requirement itself, with regard to the proper standard which should be applied to the present claims. Then, Applicants address the claims themselves.

### Restriction Practice for National Phase Applications

The instant application is a national phase application of an International PCT Application. Therefore, 37 C.F.R. §§ 1.499, 1.475, 1.143 and 1.144 apply.

Restriction practice under 35 U.S.C. § 121 and its associated rules, do not apply. See M.P.E.P. § 1895.01. Unity of invention is fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. 37 C.F.R. § 1.475. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. *Id.*

The Office Action states that ". . . the invention of Group III was found to have no special technical feature that defined the contribution over the prior art of Hillier *et al.* (GenBank Accession No. N72734, 1996) (see entire document and the sequence alignment in particular). Hilliar *et al.* teach a 447 nucleotide fragment of claimed SEQ ID NO:1 at positions (NA 3025-3295), a pT7T3D vector and a DH10B host cell". (Paper No. 12, page 14, para. 5). Applicants assert that beyond this quoted conclusion, no reasoning or explanation was provided in the Office Action as to how the prior art applies to the original claimed invention beyond its application to Group

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III, or why the claims have been restricted. This statement certainly fails to explain why the present invention was restricted into 123 different Groups. The grounds for the conclusion as to why the claims are distinct has not been set forth. Under M.P.E.P. § 816, this is required ("The particular reasons relied on by the examiner for holding that the inventions as claimed are either independent or distinct should be concisely stated. A mere statement of conclusion is inadequate.").

As Applicants have traversed the rejection, Applicants note for the record the following regarding the instant restriction requirement. Under M.P.E.P. § 803, a restriction is proper if the subject matter can be restricted into one of two or more claimed inventions, and these inventions are either independent (M.P.E.P. § 806.04) or distinct (M.P.E.P. § 806.05). However, the second element for a restriction requirement to be proper is that if the search and examination of an entire application can be made without serious burden, the examiner **must** examine it on the merits, even though it includes claims to independent and distinct inventions. Furthermore, the Office has not set forth an explanation of how a search of the claimed invention would be burdensome. Accordingly, Applicants assert that a proper restriction under M.P.E.P. § 803 has not been set forth with regard to the originally presented claims, the elections herein are provisional. The restriction should be withdrawn or, at the very least, reconsidered.

Hillier et al.

The Office Action cites Hillier et al. in support of the Restriction Requirement, stating "... the invention of Group III was found to have no special technical feature that defined the contribution over the prior art of Hillier et al. (GenBank Accession No. N72734, 1996) (see entire document and the sequence alignment in particular). Hillier et al. teach a 447 nucleotide fragment of claimed SEQ ID NO:1 at positions (NA 3025-3295), a pT7T3D vector and a DH10B host cell". With regard to Hillier et al., Applicants submit that GenBank sequence disclosed by Hillier et al. does not read on the complete  $\alpha$ 10 subunit sequences of the claimed invention. Rather, Hillier et al. merely recite a sequence fragment. Further, Hillier et al. do not teach

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the biological activity of the disclosed sequence. Hillier *et al.* only disclose that the sequence is derived from human multiple sclerosis lesions. There is no indication that the cited fragment shares any biological activity in common with the claimed sequences or any indication that the fragment of Hillier *et al.* relates to the claimed sequences comprising the  $\alpha 10$  subunit with or without the splicing region. Thus, the claims of the present invention share technical features that define a contribution over the art. However, in the interest of expediting prosecution, the claims have been amended herein to recite specific fragments of the  $\alpha 10$  subunit.

Applicants respectfully submit that all of the claims of the present invention, in all 123 Groups, form one single invention concept and share a technical relationship, that of the integrin subunit  $\alpha 10$ . The claims of the present invention are all directed to isolated polypeptides and polynucleotides of  $\alpha 10$ , methods of making the polypeptides of  $\alpha 10$ , binding entities of  $\alpha 10$  and recombinant or isolated integrin heterodimers comprising  $\alpha 10$  and methods of using  $\alpha 10$  as a marker or target. Accordingly, a special technical feature exists at least with all of the claims.

However, in the interest of expediting prosecution, Application invite the Examiner to consider the rejoinder of certain Groups, if all 123 Groups are not rejoined, and provide the following comments to that regard.

First, Applicants request that the claims directed to the amino acid sequences and those directed to nucleic acid sequences be examined together. Applicants submit that the amino acids sequences and the nucleic acid sequences of the claimed invention share the same technical features by definition, as the nucleic acid sequences encode for their corresponding amino acid sequences. Similarly, by having possession of the amino acid sequences, the skilled artisan would by definition have possession of the corresponding nucleotide sequences. Thus, Applicants submit that the technical features that define a contribution which the claimed inventions, considered as a whole, makes over the prior art are shared by both the amino acid and nucleic acid sequences, and thus the unity of invention requirement is met. Further, there is additional burden placed on the Examiner for

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searching both types of sequences, as by searching one, the Examiner will by definition have searched the other.

Next, Applicants respectfully request that those groups concerning the full length  $\alpha 10$  amino acid sequence be rejoined (*i.e.*, those Groups concerning SEQ ID NO:2, Group I, as well as Groups III, VI, VIII, X, XII, XIV, XVI, XVIII, XIX, XXIII, XXV, XXVI, XXVII, XXVII, XXVIII, XXIX, XXXV, XXXVIII, XXXIX, XL, XLII, XLV, XLVI, XLVII, XLIX, LII, LIII, LIV, LV, LVII, LVIII, LIX, LXI, LXXIV, LXXVI, LXXIX, LXXX, LXXXI, LXXXIII, LXXXVI, LXXXVII, LXXXVIII, XC, XCI, XCII and XCIV). Applicants submit that the technical features that define a contribution which the claimed inventions, considered as a whole, make over the prior art are shared by these Groups, *i.e.*, all these Groups relate to the integrin  $\alpha 10$  sequence and methods of using it. Applicants also request that those groups concerning the  $\alpha 10$  sequence without the splice region be rejoined (*i.e.*, those Groups concerning SEQ ID NO:4, Group II, as well as Groups IV, VII, IX, XI, XIII, XV, XVII, XX, XXI, XXIV, XXX, XXXI, XXXII, XXXIII, XXXIV, XXXVI, XLI, XLIII, XLVIII, L, LX, LXII, LXIV, LXXV, LXXVII, LXXXII, LXXXIV, XCIII and XCV). Applicants submit that the technical features that define a contribution which the claimed inventions, considered as a whole, make over the prior art are shared by these Groups, *i.e.*, all these Groups relate to the integrin  $\alpha 10$  sequence, without the splice region, and methods of using it.

Applicants further invite the Examiner to consider the rejoinder of the following Groups of claims.

Applicants request the rejoinder of the claims directed to polypeptides of the invention with the claims directed to methods/processes of providing an integrin subunit (Groups XIX, XXI, XXII) or specific fragments thereof (Groups XXXVIII, XXXIX, XXXVII). Similarly, Applicants request the rejoinder of the claims directed to polypeptides of the  $\alpha 10$  subunit with the claims directed to methods of using the  $\alpha 10$  subunit (Groups XL, XLII, XLV, XLVI, XLI, XLIII, XLIV).

Applicants further request rejoinder of those claims directed to binding entities, with those claims directed to methods of using the binding entities (XLVII,

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XLIX, LII, LIII, XLVIII, L, LXII, LXI and LI) and methods of detecting binding entities (LXV and LXVI).

Similarly, the claims directed to polypeptides of the  $\alpha$ 10 subunit may be rejoinder with the claims directed to methods of using the  $\alpha$ 10 subunit, with or without the  $\beta$  subunit for purposes of determining different stages of cell development (Groups LV, LVII, LVIII and LVI), methods of detecting the  $\alpha$ 10 subunit (Groups LIV), methods of using the  $\alpha$ 10 subunit as a marker or target (LIX, LX).

Applicants request the rejoinder of Groups VI, VIII, X, XII, XIV and XVI. These Groups all concern binding entities which can specifically bind to the  $\alpha$ 10 subunit of SEQ ID NO:2. The Office Action has restricted the Groups bases on the binding entity of use. However, Applicants note that the binding entities in question, proteins, carbohydrates, antibodies, peptides, lipids and ligands are technically all ligands. Further, a binding entity is by definition a protein. To this end Applicants also request the rejoinder of Groups VII, IX, XI, XIII, XV and XVII, which all concern binding entities which can specifically bind to the  $\alpha$ 10 subunit of SEQ ID NO:4.

Thus, at least for the reasons addressed above, Applicants request reconsideration of the restriction.

### III. Election of Species

The Office Action states that Applicants must elect a species to which claims will be restricted if no generic claim is held to be allowable.

Applicants disagree regarding the distinctness of the fragments of the  $\alpha$ 10 subunit relative to the invention, i.e., all are part of the  $\alpha$ 10 subunit. Moreover, Applicants assert that there would be no undue burden to search all the fragments, as the entire  $\alpha$ 10 sequence has already been searched.

Again, Applicants state that restriction practice in both international and national stage applications is determined under unity of invention principles as set forth in 37 C.F.R. §§ 1.475 and 1.499 as discussed above. Restriction practice under 35 U.S.C. § 121 is *not* applicable to either international or national stage applications.

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Regarding the search and examination of these four compounds, Applicants direct the Examiner's attention to M.P.E.P. § 803 which states: "If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent and distinct inventions." No basis as to why a search of these categories would be burdensome, let alone seriously burdensome, was set forth in the action. Accordingly, Applicants respectfully request withdrawal of the restriction.

CONCLUSION

This is believed to be in full response to the outstanding Restriction Requirement. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned at the Examiner's earliest convenience.

Respectfully submitted,

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**Attachment to Amendment and Reply to Restriction Requirement**

**Marked-up Claims 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 15-18, 20, 23-25, 27-31, 33-35, 46, 48-50, 52, 54, 56-59, 73, 76, 78-80, 82, 84-86, 88-90, 99, 101-103, 107, 110-112 and 127-136**

2. (Twice Amended) A process of producing a recombinant integrin subunit  $\alpha 10$  comprising essentially the amino acid sequence shown in SEQ ID No. 2 or SEQ ID No. 4 or homologues [or fragments] thereof or a fragment selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain, having essentially the same biological activity, which process comprises the steps of

- a) isolating a polynucleotide comprising a nucleotide sequence coding for an integrin subunit  $\alpha 10$ , or homologues [or fragments] thereof or a fragment having essentially the same biological activity,
- b) constructing an expression vector comprising the isolated polynucleotide,
- c) transforming a host cell with said expression vector,
- d) culturing said transformed host cell in a culture medium under conditions suitable for expression of integrin subunit  $\alpha 10$ , or homologues or I domain or fragment[s] thereof having essentially the same biological activity, in said transformed host cell, and, optionally,
- e) isolating the integrin subunit  $\alpha 10$ , or homologues or fragments thereof having essentially the same biological activity, from said transformed host cell or said culture medium;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

3. (Amended) A process of providing an integrin subunit  $\alpha 10$ , or homologues or fragment[s] thereof having essentially the same biological activity, whereby said subunit is isolated from a cell in which it is naturally present;

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wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

4. (Twice Amended) An isolated polynucleotide comprising a nucleotide coding for an integrin subunit  $\alpha 10$ , or for homologues or fragment[s] thereof having essentially the same biological activity, which polynucleotide comprises essentially the nucleotide sequence shown in SEQ ID No. 2 or SEQ ID No. 4 or suitable parts thereof:

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

5. (Amended) An isolated polynucleotide or oligonucleotide which hybridises to a DNA or RNA coding for an integrin subunit  $\alpha 10$ , or for homologues or fragment[s] thereof having essentially the same biological activity, wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$ :

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

6. (Twice Amended) A vector comprising a polynucleotide or oligonucleotide coding for an integrin subunit  $\alpha 10$ , or for homologues or fragment[s] thereof having essentially the same biological activity, which polynucleotide or oligonucleotide comprises essentially the nucleotide sequence shown in SEQ ID No. 2 or SEQ ID No. 4 parts thereof:

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

7. (Amended) A vector comprising a polynucleotide or oligonucleotide which hybridises to a DNA or RNA coding for an integrin subunit  $\alpha 10$ , or for

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homologues or fragment[s] thereof, wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$ :

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

9. (Twice Amended) A cell generated by steps a) to d) of the process as defined in claim 2, in which a polynucleotide or oligonucleotide coding for an integrin subunit  $\alpha 10$ , or for homologues or fragment[s] thereof having essentially the same biological activity, which polynucleotide or oligonucleotide comprises the nucleotide sequence shown in SEQ ID No. 2 or SEQ ID No. 4 or parts thereof, has been stably integrated in the cell genome:

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

10. (Twice Amended) Binding entities having the capability of binding specifically to an integrin subunit  $\alpha 10$  comprising the amino acid sequence of SEQ ID No. 2 or SEQ ID No. 4, or to homologues or fragment[s] thereof:

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

11. (Amended) Binding entities according to claim 10, which are chosen from the group comprising proteins, peptides, carbohydrates, lipids, and natural integrin binding ligands, and fragments thereof.

12. (Amended) Binding entities according to claim 10, which are polyclonal or monoclonal antibodies, or fragments thereof.

13. (Twice Amended) A recombinant or isolated integrin heterodimer comprising a subunit  $\alpha 10$  and a subunit b, in which the subunit  $\alpha 10$  comprises essentially the amino acid sequence shown in SEQ ID No. 2 or SEQ ID No. 4, and

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homologues and a fragment[s] thereof having essentially the same biological activity;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

15. (Twice Amended) A process of producing a recombinant Integrin heterodimer comprising a subunit  $\alpha$ 10 and a subunit  $\beta$ , in which the subunit  $\alpha$ 10 comprises essentially the amino acid sequence shown in SEQ ID No. 2 and SEQ ID No. 4, homologues and a fragment[s] thereof having essentially the same biological activity, which process comprises the steps of

- a) isolating one polynucleotide comprising a nucleotide sequence coding for a subunit  $\alpha$ 10 of an integrin heterodimer and, optionally, another polynucleotide comprising a nucleotide sequence coding for a subunit  $\beta$  of an integrin heterodimer, or polynucleotides or oligonucleotides coding for homologues or fragment[s] thereof having essentially the same biological activity,
- b) constructing an expression vector comprising said isolated polynucleotide coding for said subunit  $\alpha$ 10 optionally in combination with an expression vector comprising said isolated nucleotide coding for said subunit  $\beta$ ,
- c) transforming a host cell with said expression vector or vectors,
- d) culturing said transformed host cell in a culture medium under conditions suitable for expression of an integrin heterodimer comprising a subunit  $\alpha$ 10 and a subunit  $\beta$ , or homologues or fragment[s] thereof having essentially the same biological activity, in said transformed host cell, and, optionally,
- e) isolating the integrin heterodimer comprising a subunit  $\alpha$ 10 and a subunit  $\beta$ , or homologues or fragment[s] thereof having essentially the same biological activity, or the  $\alpha$ 10 subunit thereof from said transformed host cell or said culture medium;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

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16. (Amended) A process of providing a integrin heterodimer comprising a subunit  $\alpha 10$  and a subunit  $\beta$ , or homologues or fragment[s] thereof having essentially the same biological activity, whereby said integrin heterodimer is isolated from a cell in which it is naturally present;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

17. (Twice Amended) A cell containing a first vector, said first vector comprising a polynucleotide or oligonucleotide coding for a subunit  $\alpha 10$  of an integrin heterodimer, or for homologues or parts thereof having essentially the same biological activity, which polynucleotide or oligonucleotide comprises essentially the nucleotide sequence shown in SEQ ID No. 2 or SEQ ID No. 4 or parts thereof, and a second vector, said second vector comprising a polynucleotide or oligonucleotide coding for a subunit  $\beta$  of an integrin heterodimer, or for homologues or fragment[s] thereof having essentially the same biological activity;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

18. (Amended) Binding entities having the capability of binding specifically to an integrin heterodimer comprising a subunit  $\alpha 10$  and a subunit  $\beta$ , or to homologues or fragment[s] thereof having essentially the same biological activity, or an subunit  $\alpha 10$  thereof, having essentially the same biological activity;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

20. (Twice Amended) Binding entities according to claim 18, which are chosen among the group comprising proteins, peptides, carbohydrates, lipids, and natural integrin binding ligands, and fragments thereof.

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23. (Twice Amended) A fragment [according to claim 22] of the integrin subunit  $\alpha$ 10, [which is] wherein the fragment is a peptide comprising the amino acid sequence SEQ ID No. 7.

24. (Twice Amended) A fragment [according to claim 22] of the integrin subunit  $\alpha$ 10, [which is] wherein the fragment is the amino acid sequence from about amino acid No. 952 to about amino acid no. 986 of SEQ ID No. 2.

25. (Twice Amended) A fragment [according to claim 22] of the integrin subunit  $\alpha$ 10, [which is] wherein the fragment is the amino acid sequence from about amino acid No. 140 to about amino acid no. 337 of SEQ ID No. 2.

26. (Twice Amended) A method of producing a fragment of the integrin subunit  $\alpha$ 10 wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain [as defined in claim 22], which method comprises a sequential addition of amino acids containing protective groups.

27. (Twice Amended) A polynucleotide or oligonucleotide coding for a fragment selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain of the integrin subunit  $\alpha$ 10 [as defined in claim 22].

28. (Twice Amended) Binding entities having the capability of binding specifically to a fragment of the human integrin subunit  $\alpha$ 10 wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain [as defined in claim 22].

29. (Amended) Binding entities according to claim 28, which are chosen from the group comprising proteins, peptides, carbohydrates, lipids, and natural integrin binding ligands, and fragments thereof.

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30. (Amended) Binding entities according to claim 28, which are polyclonal or monoclonal antibodies, or fragments thereof.

31. (Thrice Amended) A method of using an integrin subunit  $\alpha 10$  *in vitro* comprising using the amino acid sequence shown in SEQ ID No. 2, SEQ ID No. 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or a homologue or fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues expressing said integrin subunit  $\alpha 10$ , wherein the cells or tissues are of animal including human origin;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

33. (Thrice Amended) A method of using an integrin subunit  $\alpha 10$  *in vitro* comprising using the amino acid sequence shown in SEQ ID No. 2, SEQ ID No. 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or a homologue or fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues expressing said integrin subunit  $\alpha 10$ , wherein the cells or tissues are of animal including human origin [The method of claim 31], whereby said fragment is a peptide comprising the amino acid sequence SEQ ID NO: 7.

34. (Thrice Amended) A method of using an integrin subunit  $\alpha 10$  *in vitro* comprising using the amino acid sequence shown in SEQ ID No. 2, SEQ ID No. 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or a homologue or fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues expressing said integrin subunit  $\alpha 10$ , wherein the cells or tissues are of animal including human origin [The method of claim 31], whereby said fragment comprises the amino acid

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sequence from about amino acid no. 952 to about amino acid no. 986 of No. of SEQ ID NO: 2.

35. (Thrice Amended) A method of using an integrin subunit  $\alpha 10$  in vitro comprising using the amino acid sequence shown in SEQ ID No. 2, SEQ ID No. 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or a homologue or fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues expressing said integrin subunit  $\alpha 10$ , wherein the cells or tissues are of animal including human origin [The method of claim 31], whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid no. 337 of SEQ ID NO: 1.

46. (Thrice Amended) A method of using binding entities having the capability of binding specifically to an integrin subunit  $\alpha 10$  in vitro, comprising using an amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit or to homologues or fragment[s] thereof having essentially the same biological activity, as markers or target molecules of cells or tissues expressing said integrin subunit  $\alpha 10$ , wherein the cells or tissues are of animal including human origin;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

48. (Thrice Amended) A method of using binding entities having the capability of binding specifically to an integrin subunit  $\alpha 10$  in vitro, comprising using an amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit or to homologues or fragment thereof having essentially the same biological activity, as markers or target molecules of cells or tissues expressing said integrin subunit  $\alpha 10$ , wherein the cells

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or tissues are of animal including human origin [The method of claim 46], whereby said fragment is a peptide comprising the amino acid sequence SEQ ID NO: 7.

49. (Thrice Amended) A method of using binding entities having the capability of binding specifically to an integrin subunit  $\alpha 10$  in vitro, comprising using an amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit or to homologues or fragment thereof having essentially the same biological activity, as markers or target molecules of cells or tissues expressing said integrin subunit  $\alpha 10$ , wherein the cells or tissues are of animal including human origin [The method of claim 46], [were] wherein said fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID NO: 2.

50. (Thrice Amended) A method of using binding entities having the capability of binding specifically to an integrin subunit  $\alpha 10$  in vitro, comprising using an amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit or to homologues or fragment thereof having essentially the same biological activity, as markers or target molecules of cells or tissues expressing said integrin subunit  $\alpha 10$ , wherein the cells or tissues are of animal including human origin [The method of claim 46], whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid No. 337 of SEQ ID NO: 2.

52. (Four Times Amended) The method of claim 46, comprising detecting the presence of an integrin subunit  $\alpha 10$  comprising the amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4 or of an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or of homologues or fragment[s] thereof having essentially the same biological activity:

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

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54. (Thrice Amended) A method for detecting the presence of a integrin subunit  $\alpha 10$ , or of a homologue or fragment of said integrin subunit having essentially the same biological activity, on cells, comprising using a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID NO: 2 as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$ :

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

56. (Twice Amended) [The method of claim 54] A method for detecting the presence of a integrin subunit  $\alpha 10$ , or of a homologue or fragment of said integrin subunit having essentially the same biological activity, on cells, comprising using a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID NO: 2 as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$ , whereby said fragment is a peptide [chosen] selected from the group [comprising] consisting of peptides of the cytoplasmic domain, the I-domain and the spliced domain.

57. (Thrice Amended) [The method of claim 54] A method for detecting the presence of a integrin subunit  $\alpha 10$ , or of a homologue or fragment of said integrin subunit having essentially the same biological activity, on cells, comprising using a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID NO: 2 as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$ , whereby said fragment peptide comprising the amino acid sequence SEQ ID NO: 7.

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58. (Thrice Amended) [The method of claim 54] A method for detecting the presence of a integrin subunit  $\alpha 10$ , or of a homologue or fragment of said integrin subunit having essentially the same biological activity, on cells, comprising using a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID NO: 2 as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$ , whereby said fragment comprises the amino acid sequence from about amino acid No. 952 to about amino acid no. 986 of SEQ. ID NO: 2.

59. (Twice Amended) [The method of claim 54] A method for detecting the presence of a integrin subunit  $\alpha 10$ , or of a homologue or fragment of said integrin subunit having essentially the same biological activity, on cells, comprising using a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID NO: 2 as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$ , whereby said fragment comprises the amino acid sequence from about amino acid No. 140 to about amino acid No. 337 of SEQ ID NO: 1.

73. (Amended) A pharmaceutical composition comprising as an active ingredient a pharmaceutical agent or an antibody which is capable of using an integrin heterodimer comprising a subunit  $\alpha 10$  and a subunit b, or the subunit  $\alpha 10$  thereof, or a homologue or fragment of said integrin or subunit  $\alpha 10$  having essentially the same biological activity, as a target molecule:

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

76. (Amended) A vaccine comprising as an active ingredient an integrin heterodimer comprising a subunit  $\alpha 10$  and a subunit b, or the subunit  $\alpha 10$  thereof, or

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a homologue or fragment of said integrin or subunit  $\alpha 10$ , or DNA or RNA coding for said integrin subunit  $\alpha 10$ :

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

78. (Thrice Amended) A method of using binding entities having the capability of binding specifically to an integrin subunit  $\alpha 10$  *in vitro* comprising binding the amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$  or to homologues or fragment[s] thereof having essentially the same biological activity, for promoting adhesion of chondrocytes and/or osteoblasts to surfaces of implants to stimulate osseointegration;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

79. (Twice Amended) A method of detecting the presence of integrin binding entities *in vitro*, comprising interacting an integrin heterodimer comprising a subunit  $\alpha 10$  and a subunit  $\beta$ , or the subunit  $\alpha 10$  thereof, or a homologue or fragment of said integrin or subunit having essentially the same biological activity, with a sample, thereby causing said integrin, subunit  $\alpha 10$ , or homologue or fragment thereof, to modulate the binding to its natural ligand or other proteins present in said sample:

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

80. (Twice Amended) A method of studying consequences of the interaction of a human heterodimer integrin *in vitro*, comprising interacting a subunit  $\alpha 10$  and a subunit  $\beta$ , or the subunit  $\alpha 10$  thereof, or a homologue or fragment of said integrin or subunit having essentially the same biological activity, with an integrin binding entity and thereby initiating a cellular reaction;

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wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

82. (Twice Amended) A method of using DNA or RNA *in vitro*, comprising encoding an integrin subunit  $\alpha 10$  or homologues or fragment[s] thereof as a target molecule;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

84. (Twice Amended) A method of using a human heterodimer integrin *in vitro*, comprising using a subunit  $\alpha 10$  and a subunit  $\beta$ , or the subunit  $\alpha 10$  thereof, or a homologue or fragment of said integrin or subunit, or a DNA or RNA encoding an integrin subunit  $\alpha 10$  or homologues or fragments thereof, as a marker or target molecule during angiogenesis;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

85. (Amended) A pharmaceutical composition comprising as an active ingredient a pharmaceutical agent of antibody which is capable of stimulating cell surface expression of an integrin heterodimer comprising a subunit  $\alpha 10$  and a subunit  $\beta$ , or the subunit  $\alpha 10$  thereof, or a homologue or fragment of said integrin or subunit  $\alpha 10$  having essentially the same biological activity;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

86. (Thrice Amended) A method of using a collagen binding integrin subunit  $\alpha 10$  comprising using the amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or a homologue or fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues

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expressing said integrin subunit  $\alpha$ 10, which cells or tissues are of animal including human origin;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

88. (Thrice Amended) A method of using a collagen binding integrin subunit  $\alpha$ 10 comprising using the amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha$ 10 and a subunit  $\beta$ , or a homologue or fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues expressing said integrin subunit  $\alpha$ 10, which cells or tissues are of animal including human origin [The method of claim 86], whereby said fragment is a peptide comprising the amino acid sequence SEQ ID NO: 7.

89. (Thrice Amended) A method of using a collagen binding integrin subunit  $\alpha$ 10 comprising using the amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha$ 10 and a subunit  $\beta$ , or a homologue or fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues expressing said integrin subunit  $\alpha$ 10, which cells or tissues are of animal including human origin [The method of claim 86], whereby said fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID NO: 2.

90. (Thrice Amended) A method of using a collagen binding integrin subunit  $\alpha$ 10 comprising using the amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha$ 10 and a subunit  $\beta$ , or a homologue or fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues expressing said integrin subunit  $\alpha$ 10, which cells or tissues are of animal including

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human origin [The method of claim 86], whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid no. 337 of SEQ ID NO: 2.

99. (Thrice Amended) A method of using binding entities having the capability of binding specifically to an integrin subunit  $\alpha 10$  comprising using the amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or to homologues or fragment[s] thereof having essentially the same activity, as markers or target molecules of cells or tissues expressing said integrin subunit  $\alpha 10$ , which cells or tissues are of animal including human origin;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

101. (Thrice Amended) A method of using binding entities having the capability of binding specifically to an integrin subunit  $\alpha 10$  comprising using the amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or to homologues or fragment[s] thereof having essentially the same activity, as markers or target molecules of cells or tissues expressing said integrin subunit  $\alpha 10$ , which cells or tissues are of animal including human origin [The method of claim 99], whereby said fragment is a peptide comprising the amino acid sequence SEQ ID No. 7.

102. (Thrice Amended) A method of using binding entities having the capability of binding specifically to an integrin subunit  $\alpha 10$  comprising using the amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or to homologues or fragment[s] thereof having essentially the same activity, as markers or target molecules of cells or tissues expressing said integrin subunit  $\alpha 10$ , which cells or tissues are of animal including human origin [The method of claim 99], whereby said

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fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID NO: 2.

103. (Thrice Amended) A method of using binding entities having the capability of binding specifically to an integrin subunit  $\alpha 10$  comprising using the amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or to homologues or fragment[s] thereof having essentially the same activity, as markers or target molecules of cells or tissues expressing said integrin subunit  $\alpha 10$ , which cells or tissues are of animal including human origin [The method of claim 99], whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid No. 337 of SEQ ID NO: 2.

105. (Four Times Amended) The method of claim 99, further comprising detecting the presence of an integrin subunit  $\alpha 10$  comprising the amino acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4, or of an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or of homologues or fragment[s] thereof having essentially the same biologically activity;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

107. (Thrice Amended) A method of detecting the presence of an integrin subunit  $\alpha 10$ , or of a homologue or fragment of said integrin subunit having essentially the same activity, on cells, using a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID NO: 2 as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$ ;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

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110. (Thrice Amended) A method of detecting the presence of an integrin subunit  $\alpha 10$ , or of a homologue or fragment of said integrin subunit having essentially the same activity, on cells, using a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID NO: 2 as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$  [The method of claim 107], whereby said fragment is a peptide comprising the amino acid sequence SEQ ID NO: 7.

111. (Thrice Amended) A method of detecting the presence of an integrin subunit  $\alpha 10$ , or of a homologue or fragment of said integrin subunit having essentially the same activity, on cells, using a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID NO: 2 as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$  [The method of claim 107], whereby said fragment comprises the amino acid sequence from about amino acid No. 952 to about amino acid no. 986 of SEQ ID No. 2.

112. (Thrice Amended) A method of detecting the presence of an integrin subunit  $\alpha 10$ , or of a homologue or fragment of said integrin subunit having essentially the same activity, on cells, using a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID NO: 2 as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$  [The method of claim 107], whereby said fragment comprises the amino acid sequence from about amino acid No. 140 to about amino acid No. 337 of SEQ ID NO: 2.

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127. (Thrice Amended) A method of using binding entities having the capability of binding specifically to an integrin subunit  $\alpha 10$  comprising using the amino acid sequence shown in SEQ ID No. 2 or SEQ ID No. 4, or an integrin heterodimer comprising said subunit  $\alpha 10$  and a subunit  $\beta$ , or to homologues or fragments thereof having essentially the same biological activity, for promoting adhesion of chondrocytes, and/or osteoblasts to surfaces of implants to stimulate osseointegration;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

128. (Twice Amended) A method of using an integrin heterodimer as a target for anti-adhesive drugs or molecules in tendon, ligament, skeletal muscle, or other tissues, comprising using an integrin subunit  $\alpha 10$  and a subunit  $\beta$ , or the subunit  $\alpha 10$  and a subunit  $\beta$ , or the subunit  $\alpha 10$  thereof, or a homologue or fragment of said integrin or subunit  $\alpha 10$  having essentially the same biological activity, as a target for anti-adhesive drugs or molecules in tendon, ligament, skeletal muscle, or other tissues where adhesion impairs the function of the tissue;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

129. (Twice Amended) A method of stimulating, inhibiting, or blocking the formation of cartilage or bone, comprising administering to a subject a suitable amount of a pharmaceutical agent or an antibody which is capable of using an integrin heterodimer comprising a subunit  $\alpha 10$  and a subunit  $\beta$ , or the subunit  $\alpha 10$  thereof, or a homologue or fragment of said integrin or subunit  $\alpha 10$  having essentially the same biological activity, as a target molecule;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

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130. (Twice Amended) A method of preventing adhesion between tendon/ligaments and the surrounding tissue after infection, inflammation, and after surgical intervention where adhesion impairs the function of the tissue, comprising administering to a subject a suitable amount of a pharmaceutical agent or an antibody which is capable of using an integrin heterodimer comprising a subunit  $\alpha 10$  and a subunit  $\beta$ , or the subunit  $\alpha 10$  thereof, or a homologue or fragment of said integrin or subunit  $\alpha 10$  having essentially the same biological activity, as a target molecule;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

131. (Twice Amended) A method of stimulating extracellular matrix synthesis and repair by activation or blockage of an integrin heterodimer comprising using a subunit  $\alpha 10$  and a subunit  $\beta$  or of the subunit  $\alpha 10$  thereof or of a homologue or fragment of said integrin, or subunit  $\alpha 10$  having essentially the same biological activity;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

132. (Twice Amended) A DNA encoding an integrin subunit  $\alpha 10$  or homologues or fragment[s] thereof as a target molecule;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

133. (Twice Amended) The method according to claim 132, whereby a polynucleotide or oligonucleotide hybridises to the DNA or RNA encoding an integrin subunit  $\alpha 10$  or homologues or fragments thereof and whereby said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit  $\alpha 1$ ;

wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

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134. (Twice Amended) A method of using a human heterodimer integrin comprising using a subunit  $\alpha 10$  and a subunit  $\beta$ , or the subunit  $\alpha 10$  thereof, or a homologue or fragment of said integrin or subunit having essentially the same biological activity, or a DNA or RNA encoding an integrin subunit  $\alpha 10$  or homologues or fragments thereof, as a marker or target molecule during angiogenesis;  
wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

135. (Amended) An RNA encoding an integrin subunit  $\alpha 10$  or homologues or fragments thereof as a target molecule;  
wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.

136. (Amended) A method of using DNA or RNA encoding an integrin subunit  $\alpha 10$  or homologues or fragment[s] thereof as target molecules comprising: choosing cells expressing the integrin subunit  $\alpha 10$  or homologues or fragments thereof encoded by the DNA or RNA and assaying for the presence of the DNA or RNA in the cells;  
wherein the fragment is selected from the group consisting of the cytoplasmic domain, the I-domain and the spliced domain.